(MIS), growth factor 9 (GDF-9), glial-derived neurotrophic growth factor (GDNF), neurturin (NTN) and persephin.

40. (New) The isolated and purified nucleic acid molecule of claim 17 comprising a nucleotide sequence encoding an artemin polypeptide as set forth in SEQ ID NO:19.

Remarks

Claims 12, 15-18, 25, 27 and 39 have been amended, and new claim 40 has been added. Claims 12, 15-27, 39 and 40 are pending in the application. The amendments address the rejections of record in the Final Office Action of the parent application, dated November 2, 2000.

Claims 17 and 18 are rejected under 35 U.S.C. §112, first paragraph as not being enabled for a "complement" of a nucleic acid. That term has been eliminated from those claims by the foregoing amendments in order to advance the prosecution of this case. Therefore, applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 12 and 25 are rejected under 35 U.S.C. §112, second paragraph as being indefinite as to which fragment is being claimed. The amendments to claims 12 and 25 make it clear that the fragment claimed is a fragment of an artemin amino acid sequence that is naturally occurring and is at least 65% identical to SEQ ID NO:26 or a fragment thereof. It is clear, then, that the polynucleotide that is claimed is a polynucleotide that comprises a nucleic acid sequence; the nucleic acid sequence codes for a naturally occurring artemin amino acid sequence, or a fragment of a naturally occurring artemin amino acid sequence. The artemin amino acid sequence is defined by its sequence identity relative to the human artemin polypeptide sequence disclosed in SEQ ID NO:26, or its identity to a fragment of SEQ ID NO:26. This allows for the alignment of an amino acid sequence of any length ($\geq$8 amino acids) to an amino acid sequence of equal length from SEQ ID NO:26 to determine the percent identity. Thus, the nucleic acid of the claim is defined in terms of the particular amino acid sequences that it encodes. Such nucleic acids are exemplified in, e.g., SEQ ID NOs:1, 2, 6-8 and 37-39. Based on the amendment to the claims and the above discussion, applicants request withdrawal of this rejection.

Claims 16-18 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for reciting "specifically hybridizes." Applicants note that claims 16-18, as amended, do not recite the language objected to. Applicants respectfully request withdrawal of this rejection.

Claims 12, 15-16, 19-27 and 39 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which is not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention. Specifically, the language "conservatively substituted variants" of sequences listed in the claims is allegedly not supported by the specification. Applicants note that the amendments described above eliminate this language from the claims.

Further, the claims as amended meet the requirements for written description as put forth in the recently published Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, paragraph 1, "Written Description" Requirement. (Fed. Reg. 66(4), 1099-1111)(hereinafter, "Guidelines"). At page 1106, genus claims are addressed. As discussed therein, for claims drawn to a genus, the written description requirement may be satisfied by disclosing relevant, identifying characteristics sufficient to show that applicant was in possession of the claimed genus. This description does not have to be of such specificity that it would provide individual support for each species that the genus embraces. Here, applicants have defined the genus claimed by limiting the nucleic acids to those that encode the artemin amino acids defined in the claims. The amino acid sequences are defined as being structurally limited to naturally occurring and having at least 65% sequence identity with human pre-pro-artemin, as exemplified in SEQ ID NO:26. In addition, the artemin polypeptides are limited functionally to those that promote the survival of neurons. Thus, various structural and functional characteristics are used to describe the polypeptides encoded by the claimed polynucleotides. The specification, at page 16, line 5, through age 17, line 17 describes a well-known method for determining the percent identity between two sequences. Table 1 shows the percent identity between various related growth factors. The specification, at page 18, line 22 through page 20, line 2 describes the scientific basis for concluding that artemin polypeptides are expected to have sequences that are at least 65% identical. Example 1 of the specification describes the method by which artemin was discovered, and the specification discloses several nucleotide sequences that meet the limitations of the claims (SEQ ID NOs:1,2, 6-8 and 37-39). The same method can be used to isolate any nucleotides that encode naturally occurring artemin polypeptides meeting the limitations of the claims.

Based on the disclosure of the amino acid sequences of human and mouse pre-pro-artemin (SEQ ID NOS:26 and 29) and of genomic and cDNA clones that encodes artemin polypeptides (e.g. SEQ ID NOS:1, 2, 6-8 and 37-39), and the methods by which such sequences were isolated, one skilled in the art would accept that applicants were in possession of the invention as claimed. Since the amino acid sequences encoded by the claimed polynucleotides are sufficiently defined in the claims and in the specification, and since the genetic code is widely known, one skilled in the art would accept that applicants were in possession of the full genus of nucleic acids encoding the amino acid sequences. This

reasoning finds support in footnote 57 of the Guidelines, which states that "if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence." Here, not only have applicants provided a description of the amino acid sequences within the scope of the claims along with actual examples, but also, actual examples of the claimed genus of nucleotide sequences are given.

The Final Office Action, at page 4, cites *University of California v. Eli Lilly*, 119 F.3d 1559, at 1568, as supporting the assertion that the inventors did not have possession of the claimed invention at the time of filing. That case is cited as establishing that in a claim to genetic material, a generic statement does not qualify as an adequate description of the genus claimed. That case goes on to say that a generic statement "without more" is not sufficient. In that case, the claimed genus was defined *only* in terms of function ("vertebrate insulin cDNA"). Applicants contend that the claims in this case, for example claim 15, identify the genus of nucleotides claimed by more than merely a function. The nucleic acids of the instant claims are 10,000 nucleotides or less in length, and encode a naturally occurring artemin amino acid sequence which is at least 65% identical to a specifically identified sequence. In *Lilly*, the court noted that the specification and claims did not specifically define any of the genes that fall within the claimed genus, and "does not define any structural features commonly possessed by members of the genus that distinguish them from others." *Id.*, 1568. In the instant specification, from page 15, line 31 through page 20, line 10, the scientific basis for concluding that naturally occurring artemin amino acid sequences will have at least 65% sequence identity is discussed in detail. In that section, the structural features common to artemin, and other members of the same family of growth factors are described. Among these characteristics is the presence of the seven canonical framework cysteine residues. Table 1 shows the percent identity and conservation in comparisons of several GDNF-family growth factors. Similar sequence comparisons would allow the skilled artisan, without undue experimentation, to identify conserved regions among various family members, thus further defining the structural similarities. The specification, therefore, provides sufficient direction that a skilled artisan could distinguish the artemin polypeptides described in the claims from others, as required by *Lilly*. Based on the description of these amino acid sequences, the skilled artisan could reasonably be expected to envision or possess the claimed nucleotide sequences that encode such amino acid sequences. As discussed above, the Guidelines do not necessarily require an actual disclosure of the claimed nucleic acid sequences, provided the amino acid that such sequence encodes is sufficiently identified. See Guidelines, p. 1106, and footnote 57.

In addition, numerous actual examples of DNA meeting the limitations of the claims are shown. In the specification, at Example 1, methods are taught that were used successfully in identifying and isolating several of the claimed nucleotide sequences. These methods are not merely "potential

methods for isolating it," but are methods that were actually used to provide the DNA claimed. *Fiers v. Revel*, 25 USPQ2d 1601, 1606. In *Fiers*, addressing an enablement issue, the court stated that enablement "requires that the application 'contain a description that enables one skilled in the art to make and use the claimed invention.' " *Id.*, (citing *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F2d 1569, 1576). The court in that case found that a claim to "a DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide" was enabled by a disclosure that disclosed the complete nucleotide sequence of a DNA coding for beta-IF and "sets forth a detailed teaching of a method for obtaining a DNA coding for b-IF." While applicants note that the Office Action draws a distinction between the Written Description requirement and the Enablement requirement, applicants contend that where the DNA claimed is exemplified in the specification in the form of more than one *actual DNA sequences* that were identified and isolated by methods taught in detail in the specification, as in the instant case, the skilled artisan would accept that the inventors had possession of the claimed invention.

The Office Action goes on to cite *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F2d 1200, 1206, that states "when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e. until after the gene has been isolated." Here, not only does the description in both the claims and in the specification sufficiently define the claimed gene so as to distinguish it form other materials, but a method for isolating and obtaining it has also been taught and used to isolate nucleotide sequences within the claimed genus. Actual reduction to practice has indeed occurred. The methods described in the specification have been used successfully to isolate the claimed gene from two species, human and mouse. This is *not* a case where reduction to practice has not occurred. This is *not* a case where methods are recited and it is only *predicted* that such methods will lead to the isolation of the claimed DNA. This is, rather, a case where actual reduction to practice has occurred by utilizing the described methods to isolate examples of the claimed DNA. The inventors thus had possession of the claimed nucleic acids at the time of application.

In light of the foregoing, applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 12, and 15-16 are rejected under 35 U.S.C. §102(a) as being anticipated by Waterston et al. (1998), AC005038. It is alleged in the Office Action of May 18, 2000 that the cDNA sequence disclosed in Waterston et al. meets the limitations of a nucleic acid molecule that specifically hybridizes to SEQ ID NO:6. Please note that the claims have been amended to avoid defining the claimed nucleic acid sequences as "specifically hybridizing" to SEQ ID NO:6. The claims as amended

define the nucleic acid as having a length of 10,000 or less nucleotides, among other characteristics. Waterston does not meet this limitation. That reference teaches a sequence of just under 200,000 nucleotides. There is no teaching or suggestion in Waterston et al. of a sequence of 10,000 or less nucleotides. Thus, the claimed nucleic acids do not read on the sequence of Waterston et al., AC005038. Applicants therefore respectfully request reconsideration and withdrawal of this rejection

Claims 19 and 20 are rejected under 35 U.S.C. §103(a) as being unpatentable over Waterston et al. (1998). As discussed above, Waterston does not anticipate the claimed nucleic acid sequences. Thus, an expression vector containing any of the claimed nucleic acid sequences would not have been obvious to the skilled artisan. In light of the foregoing, applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 12 and 15 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for reciting the term "about." Applicants note that the claims as amended do not contain that term. Therefore, applicants respectfully request reconsideration and withdrawal of this rejection.

It is believed that the claims as amended are in condition for allowance in light of the foregoing discussion. Applicants respectfully request such action.

Respectfully submitted,

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